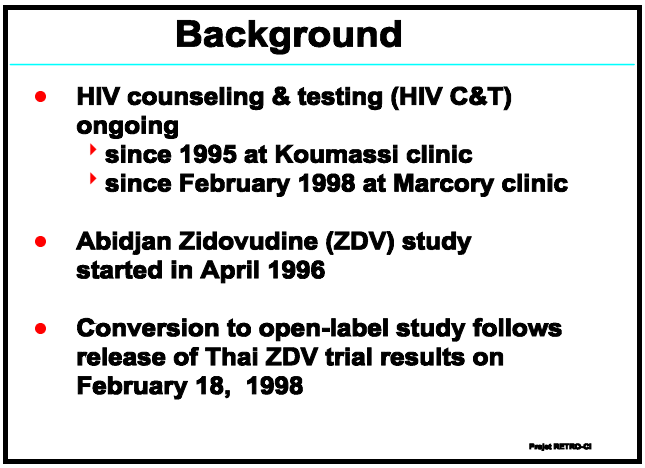
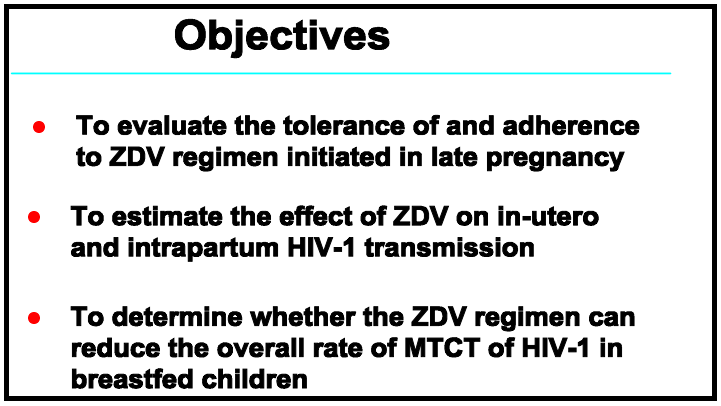
Acceptance and Compliance by Women: the Côte d'Ivoire Experience

Presented by Ehounou Ekpini, M.D.
Projet RETRO-CI

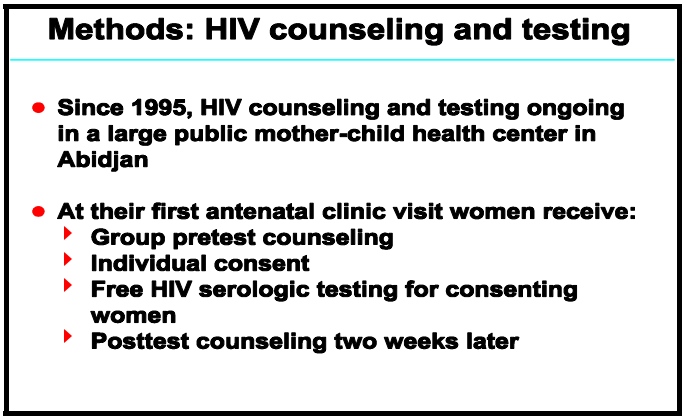
First, let me give you a background of our ongoing activities. We have implemented an HIV counseling and testing program for pregnant women at the two sites in Abidjan with whom we collaborate. This program was initiated in 1995 at the Koumassi clinic, and began only recently at the Marcory clinic.



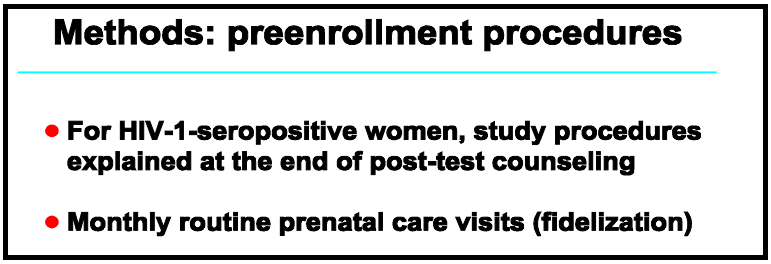
In April 1996, we started the zidovudine trial at the Koumassi clinic. In February 1998, the results of the Thai zidovudine trial were released showing a reduction of 50 percent in early HIV transmission from mother-to-child in the ZDV arm. Hence, it was no longer ethical to continue the placebo arm in the Abidjan trial, and the study was converted into an "open label" study.



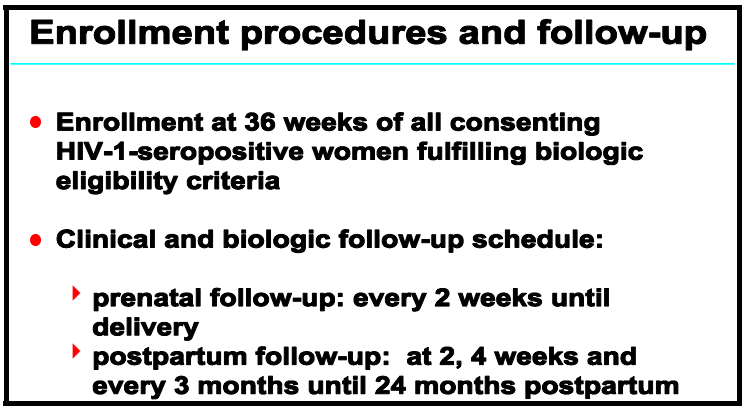
The objectives of the clinical trial were (1) to evaluate the tolerance of and adherence to a short ZDV regimen initiated in late pregnancy, (2) to estimate the effect of this regimen on in utero and intrapartum HIV-1 transmission, and (3) to determine whether the ZDV regimen can reduce the overall rate of mother-to-child transmission of HIV-1 in breast-fed children.



Since March 1995, all pregnant women attending Koumassi Mother-Child Health Center for their first antenatal visit are offered a group HIV pre-test counseling session, an individual consent form, free HIV serologic testing for those consenting, and post-test counseling 2 weeks later.



When returning 2 weeks later for the post-test counseling, women first are informed about their HIV test results and counseled about their HIV status, and then the clinical trial objectives and procedures are explained to HIV-1 seropositive women. Women who express interest in participating in the trial are seen monthly for routine prenatal care visits called "fidelization."



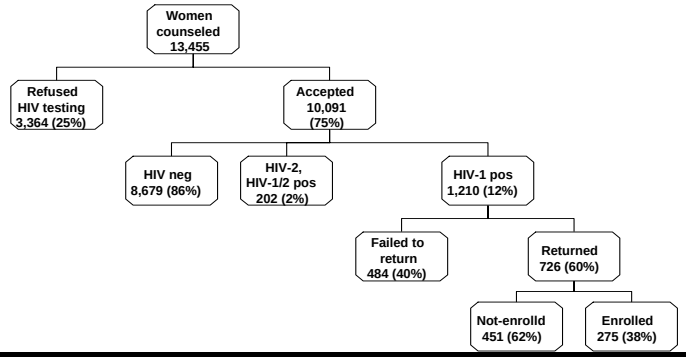
Study procedures are re-explained to consenting HIV-1-positive women who have reached 36 weeks gestational age and who fulfill biologic eligibility criteria; these women then are asked to enroll. They are followed every 2 weeks until delivery during the prenatal period and at 2 weeks, 4 weeks, and every 3 months until 24 months postpartum.

Study drug regimen

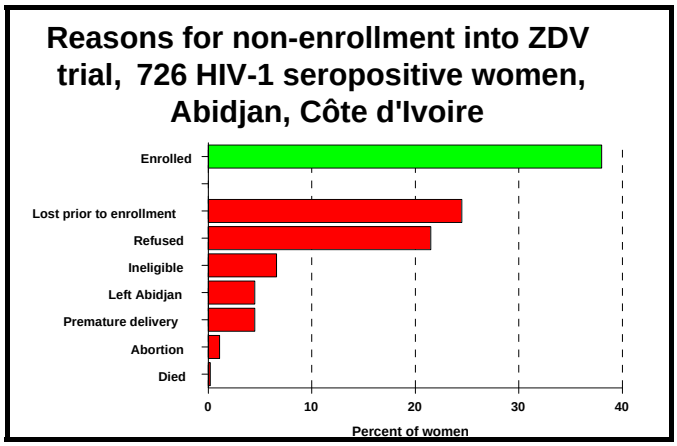
- **Prenatal regimen:**
  - **1 tablet (300 mg ZDV or placebo) orally twice daily**
- **Intra-partum regimen:**
  - **1 tablet at onset of labor followed by**
  - **1 tablet every 3 hours until delivery**
- **Post-partum regimen: none**

At enrollment, women are randomized to receive either ZDV (300 mg tablets) or placebo. They are instructed to take one tablet of study drug twice daily until the onset of labor and one tablet starting dose at the onset of labor, followed by one tablet every 3 hours until delivery. Neither mothers nor infants received ZDV in the postpartum period.

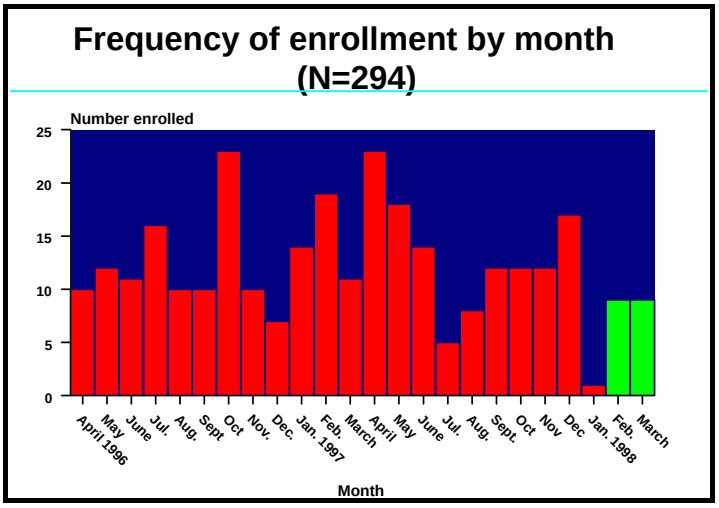
Acceptance of HIV testing, return for post-test counseling, and enrollment into trial, Apr 96 - Feb 98



This chart describes acceptance of HIV testing, return for HIV-test results, and efficiency of enrollment into the trial. Of the 13,455 women counseled during the nearly 2-year study period, 75 percent accepted testing, of whom 12 percent were HIV-1 seropositive; 60 percent returned for their HIV test results; and, finally, only 38 percent or 275 women were successfully enrolled in the randomized trial.



This figure shows the reasons for nonenrollment into the trial. "Refusal at time of post-test counseling" when the study is explained for the first time (22 percent) and "lost prior to enrollment at 36 weeks gestational age" when women start taking study drug (25 percent) were the two main reasons for nonenrollment in the trial.

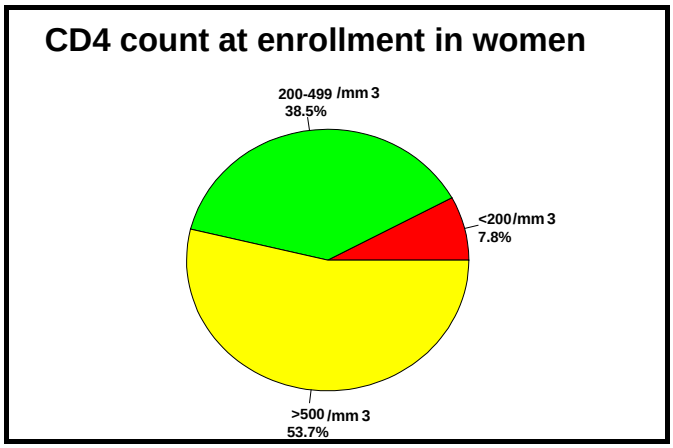


This figure shows the frequency of enrollment in the trial. As of today, 294 women have been successfully enrolled, of whom 275 were in the randomized trial and 19 in the open label part. The mean number of women enrolled monthly in the trial is about 10, even after the conversion to open label study, as shown by the last two bars at the right side of the chart.

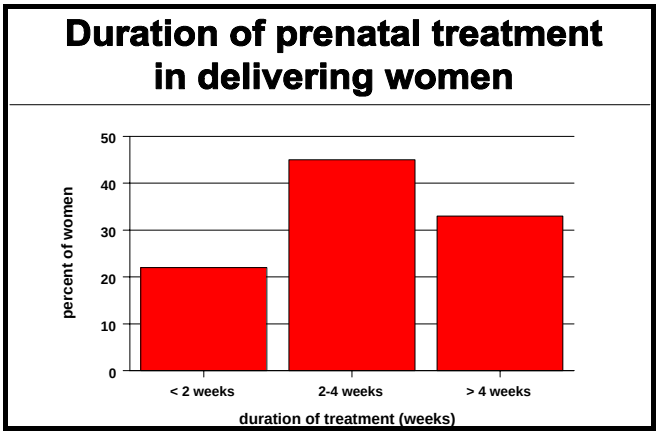
Characteristics of women at enrollment (n=275)

	Median	Range
No formal schooling	42%	.
Age (years)	26	(15-42)
Gravida	3	(1-12)
Parity	2	(0-10)
No. of prenatal visits prior to enrollment	3	(1-6)

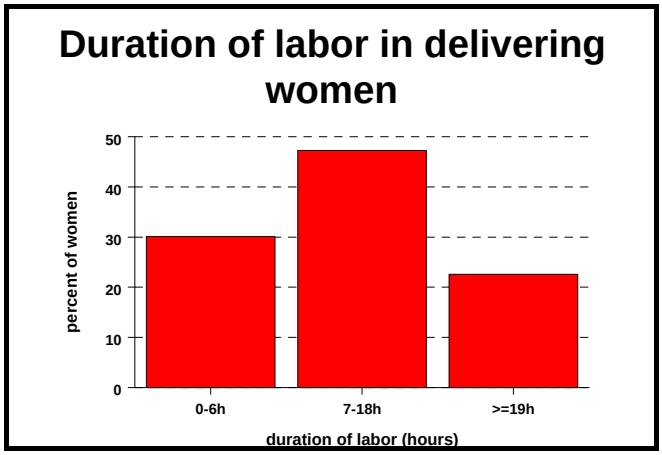
Of women enrolled in the study, the majority (42 percent) have no formal education. These women are relatively young, with a median age of 26 years and a range from 15 to 42. Their median gravidity and parity are three and two, respectively. The median number of prenatal visits completed before 36 months gestational age is three, with a range from one to six.



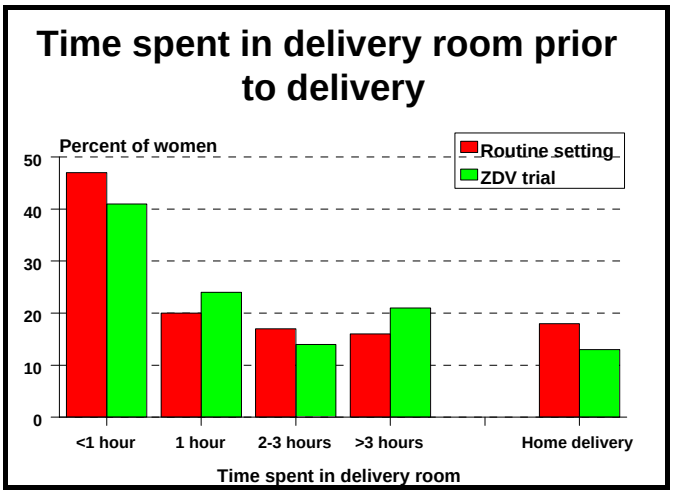
This figure shows the baseline distribution of CD4 counts in consenting women as observed at enrollment. The rate is relatively high, with 53.7 percent of women having more than 500 per μL and 38.5 percent having from 200 to 499 per μL. Only 7.8 percent of women have a CD4 count less than 200 per μL.



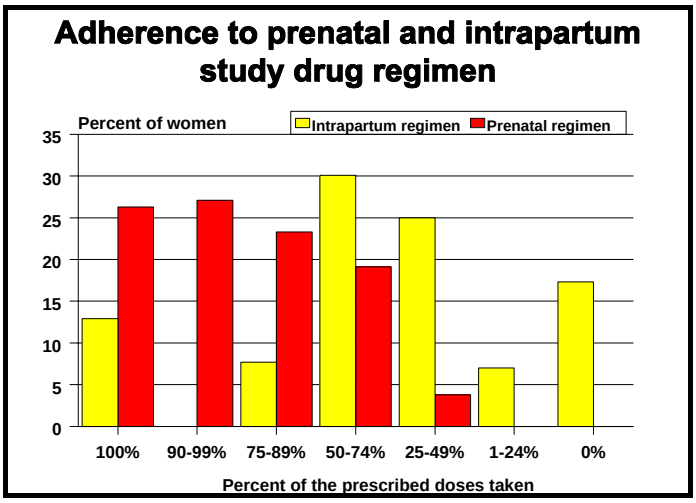
This figure shows the duration of the prenatal regimen in delivering women. The mean duration of prenatal study drug regimen was 3.9 weeks, with a range from 1 day to 11 weeks. The majority (42 percent) of women received 2 to 4 weeks of study drug, while 22 percent received less than 2 weeks.



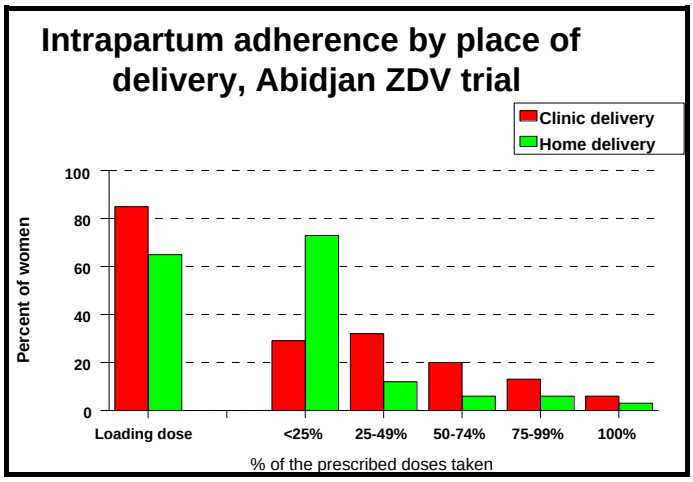
The majority of women (45 percent) had a duration of labor of 7 to 18 hours, and 30 percent of them delivered 0 to 6 hours after the onset of labor.



This chart shows the time spent by women in the delivery room prior to delivery. The single bar to the right side of the graph represents the home deliveries. Forty percent of women spent less than 1 hour in the delivery room, and 11 percent delivered at home. Overall, the median duration of labor was 10 hours.



The median percent of women who adhered to the study drug regimen during the prenatal period was 93 percent, with a range from 29 to 100 percent. Twenty-two percent of women took all of the expected prenatal doses.



This figure shows the adherence to intrapartum study drug regimen. Almost half of delivering women took less than 50 percent of their full prescribed dose. Of the women, 17.4 percent took no study drug during labor, and only 13 percent took all of the expected intrapartum dose. However, 80 percent of delivering women took the first tablet at the onset of labor, although only about 60 percent of women who delivered before arriving at the hospital took their loading dose during labor.

Grade 3 and 4 laboratory events in mothers by study arm

	Placebo arm	ZDV arm	Total
Hemoglobin	7	6	13
Granulocytes	.	.	0
Platelets	.	1	1
SGPT	1	.	1
Creatinine	.	.	0
Total	8	7	15

Grade 3 and 4 laboratory events in infants by study arm

	Placebo arm	ZDV arm	Total
Hemoglobin	12	6	18
Granulocytes	.	.	0
Platelets	1	.	1
SGPT	2	.	2
Creatinine	.	.	0
Total	15	6	21

These two figures summarize the data on tolerance of ZDV by mothers and infants. Only 15 grade 3 and 4 events, primarily anemia, were observed in this population. Overall, tolerance of ZDV is excellent in mothers. None of the women required study drug interruption, and no significant new symptoms were observed. In infants, the 21 adverse laboratory events observed were mostly anemia, as indicated by low hemoglobin level.

Follow-up status among women in randomized study (n=275)

	Before delivery	After delivery	Total (%)
Lost to follow-up	6	19	25 (9%)
Refusal	3	11	14 (5%)
Dead	1	3	4 (1.4%)

This table shows the status of the follow-up among the 275 women enrolled in the randomized study. Overall, 25 women were lost to follow-up, 14 refused the follow-up, and 4 died. Most of the refusal of follow-up (11) and of lost to follow-up (19) were in the postpartum period.

Follow-up status among children in randomized study (n=265)

	Placebo	Zidovudine	Total (%)
Lost to follow-up	8	10	18 (7%)
Refusal	5	6	11 (4%)
Dead	17	14	31 (12%)

This figure shows the status of the follow-up among children. Overall, 18 children were lost to follow-up, 11 mothers refused to bring their children for the follow-up, and 31 children died.

Causes of death among children

Causes of death	number
Obstetrical complications	16
Acute pneumonia	6
Neonatal infection	3
Malnutrition	2
Malformation	2
Others	2
Total	31

This figure shows causes of death among children in the randomized trial. A total of 31 deaths occurred in this population. Most of these deaths were due to obstetrical complications (16 children) and infectious causes (9 children), represented by acute pneumonia (6 cases) and neonatal infection (3 cases).

Conclusions

- **Adherence to study drug regimen among HIV-1 positive pregnant women is:**
  - **excellent during prenatal period**
  - **poor for the intrapartum doses**
- **Zidovudine regimen is well tolerated by mothers and infants.**
- **The majority of deaths in children are related to obstetrical complications and infectious causes reflecting the high background infant mortality**

In our experience, adherence to study drug regimen among HIV-seropositive pregnant women is excellent for the prenatal regimen, good for the first tablet at the onset of labor, but poor for the intrapartum doses. The zidovudine regimen is well tolerated by the mothers and their infants.

The majority of deaths in children are related to obstetrical complications and infectious causes, reflecting the high background infant mortality rate in this population.

I would like to finish with a general conclusion that is based on our field experience. Four main barriers exist regarding implementation of the intervention to reduce mother-to-child HIV transmission: lack of adequate prenatal care, lack of access to prenatal

HIV counseling and testing, poor acceptance of HIV counseling and testing, and poor acceptance of interventions such as the short-course regimen of ZDV.

Social-Behavioral Considerations in Acceptance and Adherence to AZT: Research and Operational Issues

Presented by Thomas Painter, Ph.D.
Centers for Disease Control and Prevention

I would like to make a few comments before I begin my presentation. Several of the workshop presentations, including mine, described a "cascade" or a series of steps through which women move toward potential access to AZT treatment to reduce mother-to-child HIV transmission.

At each step women make decisions, and at each step increasing numbers of women are lost to possible prevention options, beginning with HIV testing and moving through correct adherence to a given treatment regimen. These losses create major public health challenges.

During this workshop, several participants have expressed some frustration. We are reporting the efficacy of a short-course AZT treatment to reduce mother-to-child HIV transmission, but we still seem to lack many answers to technical questions about mother-to-child HIV transmission and about its prevention. There is some concern that this may slow the implementation of interventions in developing countries.

This is an important point. I would submit, however, that if our knowledge about biomedical and technical issues is incomplete, our knowledge in these areas is far better than our understandings about the social-behavioral issues related to women's decision-making at different points in the clinical trial process.

This reflects the fact that greater attention and resources have been focused to date on biomedical-technical issues than on social-behavioral issues. We must change this situation. The time has come to identify ways of giving greater attention to social-behavioral and organizational issues of the kind I described previously. These important but neglected issues create a wall we are very likely to run into as we try to implement some very promising medical interventions.

Now I will begin my presentation. Recall from my previous comments that in developing countries where clinical trials have assessed interventions for reducing mother-to-child transmission of HIV, including the short-course AZT regimen, the number of women that enroll in treatment interventions may represent a minority of pregnant women that are HIV-seropositive.

At five trial sites for mother-to-child HIV transmission interventions in Africa, for example, 11 to 35 percent of seropositive women were enrolled. In other words, 65 to 89

percent of seropositive women–that is, most HIV-seropositive women–were not enrolled in the trials. The reasons for these losses varied: some women elected not to participate, some were lost to follow-up, and some were determined to be ineligible.

While the trials have provided valuable evidence concerning the efficacy of various interventions, including AZT, the loss of women to prevention and treatment opportunities has important implications. First, it has negative implications for heterosexual HIV/AIDS prevention generally. Second and more directly relevant to the purposes of this workshop, these losses to prevention opportunities create obstacles and challenges to implementing interventions to reduce mother-to-child HIV transmission.

Research and operational issues needing attention can be identified at each step in the clinical trial process that follows post-test counseling. These steps include pre-enrollment and adherence to follow-up visits prior to drug treatment and enrollment and adherence to the drug treatment regimen. Dr. Ekpini and others have presented important data on how women respond to these steps within clinical trial settings.

Research issues, that is, needs for information, include the need to identify factors, processes, and mechanisms that facilitate or impede acceptance and adherence by women. Examples of social-organizational loci and issues for research include the following: First, at health service delivery points, we need to observe much more carefully how services are delivered, with particular attention to the organization, the settings, and the quality of health service delivery. As I suggested previously, we need to look more closely at the demeanor of health care staff during interactions with clients.

A second issue that needs attention concerns the personal lives of women and their partners. We need to listen to women a lot more than we have in the past, using less structured approaches to learn more about women's understanding of the treatment process and the factors that create obstacles or facilitate their acceptance and adherence to prevention and treatment opportunities.

We need to understand the effects of a multitude of so-called "normal" disruptions in the lives of women–factors such as travel, cash flow problems, and the demands of income-generating activities. These are particularly significant for women in developing countries who are increasingly playing the roles of single heads of households as well as mothers. These and other events in everyday life can conspire to disrupt the patterns of response that we expect from women when they agree to participate in prepartum follow-up visits and an AZT treatment regimen.

We also need to clarify the dynamics that occur within couple relationships that affect acceptance and adherence by women. The first process is disclosure of serostatus to partners. Certainly the situation in Africa suggests that this is a formidable obstacle. If a woman is acting as an isolated individual within a couple relationship, it makes it very difficult for her to return for visits to the clinic and to take medications once she obtains access to treatment.

The second process is the disclosure of her decision to seek treatment. This is a very big step. In a number of African trial cases we find that women simply do not tell their men,

or if they do it is extremely difficult for them.

Another issue worth looking at is the support or lack of support from partners for women's participation in treatment. In some cases we have seen some examples of men who have supported their female partners in gaining access to treatment. Examples include helping the women to remember their appointment dates for follow-up visits and helping them to remember when to take their medications. It would be interesting to look at how this works in general. My hypothesis is that in many cases women are trying to manage these things pretty much on their own in addition to taking care of children, etc.

We also need to look at issues in the surrounding social and community environments. We need to examine the impacts of wider social networks and social relations on women's decisions to accept and their ability to adhere to treatment opportunities. We need to look at the issue of broader disclosure of serostatus and the decision to seek treatment, that is, to persons other than partners.

Levels of support for participation in treatment, at least the anticipated levels, are often low. As it turns out, once people reveal their serostatus, they may find that there is more support than they expected. But there can be a wide gap between the support that women expect and what they actually receive. These perceptions affect women's decisions. A major challenge for implementing the short-course AZT treatment is to identify ways of assisting women with bridging the gap between their expectations for support and what they receive. By the same token, their partners and significant others also will need some assistance in bridging the gap between expectations and realities of acceptance and support.

As mentioned previously, we need to consider how national policies and national and local opinion shape the environments within which women make decisions to adhere to follow-up visits and treatment regimens. Examples of opinion leaders include religious leaders, ethnic group leaders, and gender- and age-based leaders.

Now let us very briefly look at some operational issues–at needs for action. In general, we need to identify approaches that will encourage and support pregnant women, their sex partners, and their significant others with their efforts to translate knowledge about serostatus into preventive and protective actions. This includes sharing information on serostatus, prevention of heterosexual HIV transmission as a means of preventing mother-to-child transmission, seeking treatment to reduce mother-to-child transmission, and adhering to treatment options.

More specifically, we need to identify strategies for addressing factors, processes, and mechanisms that affect women's responses and abilities to benefit from prevention and treatment options. Here are just a few examples: Current practice at points of health service delivery needs to be assessed. How is counseling and testing done? How are women received and welcomed at health care facilities? What is the frequency and quality of follow-up? Does it occur at the clinic only or in the home? We need to understand these processes much better.

Organizational innovations, including outreach, probably could be used to good

advantage to increase the support that women and their partners receive for seeking and accepting treatment.

As a note, the clinical trial being carried out in Bobo-Dioulasso reported some very interesting findings during a pre-trial feasibility study. Returns for post-test counseling increased substantially after a home visit by a social worker.

In a very different vein, research in eastern Africa has shown that when women were given the chance to return to a clinic for HIV test results without an appointment, return rates dropped. This suggests that the appointment process and the respect for medical authorities may engage women in a situation with which they do not feel entirely comfortable–or unconstrained. It is essential to look at ways of making this process more supportive, useful, and palatable for women.

As we move toward the implementation of these interventions, we need to look at ways of creating a tighter linkage between doing and learning. Different terms have been used to describe this: operational research, action research, etc. The terminology varies according to Anglophone or Francophone traditions. But whatever the approach, it is important to tighten the feedback loop between gathering data and using data for HIV prevention.

We also need to conduct pilot interventions. We have seen an example from Lusaka where community outreach increased the response of couples to counseling and testing opportunities. This approach merits attention, replication, and assessment. Providing more specialized training for staff is another example. Counselors need to be equipped (and motivated) to provide appropriate and high quality counseling.

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Lessons from the American Experience with Acceptance of Perinatal Prevention

Presented by Martha Rogers, M.D.
Centers for Disease Control and Prevention

I should start by saying that in the United States, after the results of the O76 trial were announced in February 1994, the CDC and National Institutes of Health got together and came up with a set of recommendations that came out from the U.S. Public Health Service. The clinical recommendations–the treatment recommendations for HIV-infected women–came out in August 1994, and the recommendations for universal HIV counseling and testing of all pregnant women in our country were published the following year in July 1995. That is essentially the beginning of the implementation, if you will, in our country.

The recommendations issued by the U.S. Public Health Service are not legally binding, that is, health care providers are not bound by those recommendations. They are simply that–recommendations. Neither CDC nor the U.S. Public Health Service is an enforcement agency in the same way as perhaps the FDA, our drug administration agency.

Some of the states, following publication of our recommendations, did, however, pass local state regulations that required doctors to provide HIV counseling and testing in their state. But most of these, while they are laws, really are not enforced. And, again, it mainly relies on the physicians and health care providers themselves to adapt the recommendations that are out there.

The major point of enforcement of good medical practice in the United States comes from malpractice insurance. If doctors are concerned about patients suing them because they did not receive particular services or because of malpractice, then that is the major enforcement of medical practice in this country. That is very different from the setting in many other countries. I just want to start by giving you that framework in which to view our success.

Given that these recommendations were issued, we established a number of studies to

begin evaluating how well the guidelines had been adopted by the medical community. I will give you a very brief overview of what we have done so far.

I am again using the slide that I used previously, which is the cascade of steps that have to take place. You now have seen this a number of times. The words on the right refer to the different studies that we have used to evaluate the different steps of the intervention.

For example, PRAMS stands for the Pregnancy Risk Assessment Monitoring System, which is conducted in 10 states by CDC's Division of Reproductive Health. It is a survey of women who have live births. It is cross-sectional and is representative of all women, not just those who are particularly at risk for HIV. So it is a survey of the general population, if you will, of women in 10 states who had live births.

The STEP Project, Surveillance To Evaluate Prevention, is a similar assessment of pregnant women, but this time dealing only with HIV-positive pregnant women, which is a much different population from the PRAMS Study.

The P-EVAL refers to the Pediatric Evaluation Project, which is a more in-depth project conducted in only four areas–Connecticut, Brooklyn, Miami, and North Carolina–and which looks at various reasons and gets much more in-depth about psychosocial issues related to acceptance of counseling, testing, and ZDV treatment.

The other way we have evaluated the guidelines is through the Survey of Childbearing Women; the slide lists it as SCBW/ZDV, which refers to blood spots on filter paper that are taken for metabolic testing of all infants born in the United States. It is done routinely in this country. We have used the collection of those samples to then look at HIV in some states. You can detect antibodies to HIV in those filter paper samples, and we developed an assay here at CDC to look also for the presence of ZDV. Some states have done that as well as part of their evaluation.

I should say that ZDV detected in the infant at birth really reflects very recent use in the mother, because the half-life of the drug is very short in women; it is somewhat longer in children, but still not that long. Thus, its presence only reflects intrapartum use of the drug and would not reflect total use of ZDV by pregnant women.

With that very brief introduction of the methods, I will give you a quick overview of what we have been seeing from the various studies.

In the United States, very, very few women do not receive prenatal care. If you look at the PRAMS study, which again was the general population of pregnant women, only 2 percent of women did not receive prenatal care. This number was fairly consistent across all of the states, and this I think is fairly representative of the United States in general.

However, among HIV-positive women, a much larger percentage of them did not receive prenatal care, about 14 percent from the STEP Project. Much of that was related to the problem that we have in this country of substance abuse among HIV-infected women. Among drug users, about 35 percent, or a third of them, did not receive adequate prenatal care. That is a major problem for us in this country–trying to get more substance-abusing women into prenatal care.

In terms of whether or not the providers offered counseling and testing, looking at the STEP data as well as the PRAMS data from the 10 states, which included both high, medium, and low HIV-prevalence states, we found that about 60 to 80 percent of physicians (and it varied from state to state and area to area) were ordering or health care providers were offering HIV counseling and testing routinely to their population of pregnant women. That, as I said, varies quite a bit.

In some places they have achieved a much higher percentage. For example, in the evaluation project of the four areas, more than 90 percent of providers offered counseling and testing. However, the 60 to 80 percent probably better represents the United States as a whole.

In terms of whether or not clients accept testing and return for their results, we found that, among the general population of pregnant women in the 10 states with PRAMS, about 75 to 85 percent of women do accept counseling and testing. Again, this is fairly high.

If you look at whether women accepted, actually got a test, and then received their result, again data indicate about 60 to 80 percent of all pregnant women in the areas that we have studied have completed these steps. That also varies widely, depending on the type of program and how well it is conducted. You will see from the Pediatric Evaluation Study that it varied anywhere from 62 to more than 95 percent of women actually getting tested, which has been seen as well in studies that have been presented in the literature here in the United States.

In terms of whether or not HIV-infected women accept ZDV in the United States, that does not seem to be a problem. Once these women have been counseled and ZDV had been recommended to them, well over 90 percent will accept the drug. We do not have a lot of data yet on how well they adhere to the regimen in this country, which is much longer than what is being offered in the Thai study. But we are beginning to collect data on that and hope to have some of that data in the future.

I will end by saying that, in addition to examining adherence to the ZDV treatment, we are also looking at how well the women and their infants get into follow-up care. I do not have any data yet to present to you on that aspect, but it is clearly something that is very important.